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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,904	01/23/1998	HARRY MEADE	TCI-028DV	2693

7590 12/17/2002

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/012,904	Applicant(s) MEADE ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21-23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21-23 and 25-30* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 19, 21-23 and 25-30 are pending in the application.

This Office Action is in response to the Amendment filed on 10/4/02.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/4/02 has been entered.

Response to Amendment

The objection to the specification has been withdrawn in light of Applicants' amendment.

The rejection of claims 19, 21, 22, 25, 27-30 under 35 U.S.C. 112, second paragraph has been withdrawn in light of Applicants' amendment of the claims.

Claims 19, 21-23, 25-30 under 35 U.S.C.103 (a) stand rejected for reasons set forth of the record mailed on 8/15/01 and further discussed below.

Claim 30 is objected to for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 103

Claims 19, 22, 23, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97).

In response to the rejection of claims 19, 22, 23 and 25-30, Applicants argue that the primary reference (Meade et al.) does not teach the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted. Applicants further argue that the secondary reference (DeBoer et al.) does not make up the deficiencies of the Meade reference because it does not teach a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which the immunoglobulin-coding sequence has been inserted. Applicants indicate that neither references teaches the alleged unique feature of the claimed construct in which there is a restriction site in between promoter and 3' non-coding sequence such that different immunoglobulin sequences can be inserted. Applicants also argue that the combination of the reference do not render claims 29 and 30 obvious because none of the references teaches a mammary epithelial cell comprising two vectors separately expressing immunoglobulin heavy chain and light chain.

Applicants' arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The teachings of Meade et al. and DeBoer et al. have been discussed in detail in the Office Action mailed on 8/15/01. Briefly, Meade et al. teaches a DNA construct for production of recombinant proteins, including immunoglobulin, comprising a promoter sequence specifically activated in mammary gland tissue, operatively linked to a DNA sequence coding for a desired recombinant protein and a 3'

non-coding sequence. DeBoer et al. teaches a construct comprising the αSi casein promoter and 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and 3' non-coding sequence. Although neither references individually teaches a DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic animal comprising a mammary gland epithelial cell specific promoter, a immunoglobulin protein-coding sequence, a 3' non-coding sequence, and a restriction site between the promoter and the 3' non-coding sequence in which the immunoglobulin coding sequence is inserted, the combination of the references renders the generation of said DNA construct obvious for the purpose of providing a vector which is amenable to accommodating the insertion of cDNAs encoding protein of interest. One of ordinary skill in the art would have been motivated to provide such modified vectors to obviate any undesirable cleavage of the cDNA inserts which intrinsically contain common restriction endonuclease recognition sites. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as tissue specific expression, and ease of insertion of various cDNAs of interest, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA constructs to obtain a DNA construct with tissue specificity, and a site for insertion of a desired cDNA into the vector without undue experimentation barring evidence to the contrary.

The Examiner agrees that neither reference teaches a mammary gland epithelial cell comprising two separate construct encoding the heavy chain and light chain of the immunoglobulin individually as claimed in claims 29 and 30. However, the claimed invention is

obvious further in view Vandamme et al. (1990, Eur. J. Biochem. Vol. 192, pp. 767-775) as discussed below.

Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., taken with DeBoer et al., (as applied to claims 19, 22, 23, and 25-28), in further view of Vandamme et al.

The teachings of Meade et al. and DeBoer et al. are discussed in the previous office action. However, they do not teach a mammary gland epithelial cell comprising two separate vectors encoding the heavy chain and light chain of the immunoglobulin.

Vandamme et al. teach the construction of a recombinant murine monoclonal antibody directed against human fibrin fragment D by co-express plasmids comprising cDNA encoding immunoglobulin light chain and heavy chain separately (see abstract, 2nd paragraph, and page 772, figure 4, page 773, 1st col., last paragraph, and 2nd col., 1st and 2nd paragraph). Vandamme et al. further teach that this antibody has very similar properties as natural antibody (see Figure 8 and 9).

It would have been obvious to one of ordinary skill in the art at the time of filing to make a mammalian epithelial cell comprising two construct separately encoding the heavy and light of the immunoglobulin operably linked to a mammalian gland specific promoter sequence because the combination teaching of Meade et al., DeBoer et al. and Vandamme et al. The obviousness to make a construct as claimed in claims 22 and 28 is discussed in the previous office action (see page 4, and page 5, 1st paragraph). The ordinary skill in the art would be motivated to put these constructs into an mammary gland epithelial cell to express the immunoglobulin protein. A

recombinant immunoglobulin needs to have both light chain and heavy chain to be functional. As such, the ordinary skill in the art would co-express the construct in the mammalian epithelial cell. The ordinary skill in the art would have reasonable expectation of success to make a functional immunoglobulin by introducing two separate constructs encoding heavy and light chain of the immunoglobulin because Vandamme et al. have shown that this can be done in CHO cells. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art when the invention was made.

Claims 19, 21-23 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97, effective filing date of 11/27/90) as applied to claims 19, 22, 23, and 25-28 above, and further in view of Bischoff et al. (FEBS Letters, 305:265-268, 1992), Buhler et al. (Bio/Technology, 9: 835-838, 1991), Gordon et al. (Bio/Technology, 5: 1183-1187, 1987), Ebert et al. (Bio/Technology, 8: 140-143, 1990), and Stinnakre et al. (FEBS Letters, 284:19-22, 1991).

In response to the rejection of claims 19, 21-23 and 25-28, Applicants argue that Bishoff et al., Buhler et al., Gordon et al., and Stinnakre et al. only teaches specific milk protein promoters and does not make up for the deficiencies of Meade et al. and DeBoer et al.

This argument has been considered but not persuasive. It would have been obvious to one of ordinary skill in the art to make a DNA construct comprising a mammary gland specific promoter, a immunoglobulin coding sequence and a mammary gland specific 3' non-translated region as discussed in the previous office action. Bishoff et al., Buhler et al., Gordon et al., and Stinnakre et al. further teaches specific milk protein promoters as claimed in claim 22, whey acid

protein promoter or the lactalbumin promoter, that are capable of direct mammary gland specific expression of heterologous protein. Substitution of one promoter with another is routine experimentation. Therefore, it would have been obvious to one of ordinary skill in the art to make the claimed DNA construct at the time of filing based on the combination of teachings from Meade et al. and DeBoer et al. Bishoff et al., Buhler et al., Gordon et al., and Stinnakre et al.

Claims 19, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316,1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076,5/27/97, effective filing date of 11/27/90) as applied to claims 19, 22, 23, and 25-28 above, and further in view of Boss et al. (U.S. Patent No. 4,816,397, 3/28/89), Bruggemann et al. (WO 90/04036, 1990), and Weidle et al. (Gene, 98:185-191, 1991).

In response to the rejection of claims 19, 22, 23, 29 and 30, Applicants argue that none of the teachings of Boss et al., Bruggemann et al. and Weidle et al. alone or in combination make up for the deficiencies of Meade et al. and DeBoer et al.

This argument is partially persuasive regard to claims 29 and 30 because none of the reference teaches a cell comprising two constructs encoding light chain and heavy chain separately. However, the above references do render the inventions of claim 19, 22 and 23 obvious for reasons set forth of the record in the previous office action. Applicants are invited to give specific reason if they think there are deficiencies.

Claim Objections

Applicant is advised that should claim 29 be found allowable, claim 30 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
December 15, 2002

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER